REMARKS

Any fees that may be due in connection with the filing of this paper or with this application may be charged to Deposit Account No. 06-1050. If a Petition for Extension of time is needed, this paper is to be considered such Petition.

Claims 1-33 and 42-44 are pending. Claims 1, 9, 13-16, 22-24, 27, 30 and 32 are amended to correct minor language inconsistencies and to clarify the claims to render it clear that the method involves introducing modified nucleic acid molecules one-by-one into host cells and individually screening each protein that is produced so that each modified protein is expressed and screened separately. This is as described in the application. For example, in the first paragraph of the "Summary," the application states:

> In practicing the methods, each molecule is individually designed, produced, processed, screened and tested in a high throughput format. Neither random or combinatorial methods nor mixtures of molecules are used.

This description is repeated throughout the summary; although in the first step, the application describes that the molecules are not necessarily individually designed, but can be prepared by any method. Once designed molecules, such as nucleic acid molecules are individually expressed, screened and tested.

Claim 24 also is amended to reintroduce a the limitations of claim 2 that inadvertently was omitted when claim 24 was rewritten as an independent claim. As originally filed, claim 24 depended from claim 2. Claim 27 similarly is amended to reintroduce the limitations of claim 9 that inadvertently were omitted when claim 27 was redrafted as an independent claims. As originally filed claim 27 depended from claim 9. Therefore, no new matter is added.

Rejection of Claims Under 35 U.S.C. §112, second paragraph

Claims 1-33 and 42-44 are rejected under 35 U.S.C. §112, second paragraph, because Reconsideration of the grounds for this rejection is respectfully requested in view of the amendments herein and the following remarks.

Claims 1-33 and 42-44

Claims 1-33 and 42-44 are rejected because each of independent claims 1, 22, 23, 24, 27, 30 and 32 allegedly recited "selecting a predetermined property from the chemical, physical and biological property." This language is alleged to be unclear.

The claims, prior to amendment herein, recited "the predetermined property is selected from among chemical, physical and biological property of the target protein," which is a recitation in the alternative. To render it more clear and to correct the grammatical error,

the claims are amended to recite "predetermined property is selected from among a chemical, a physical and a biological property of the target protein."

Claim 28

Claim 28 is rejected as indefinite in the recitation of "step (f)." Amendment of claim 27 to include the limitations of claim 9 originally present in claim 27 obviate this rejection.

THE REJECTIONS OF CLAIMS 1-21, 27 AND 42-44 UNDER 35 U.S.C. §102

Claims 1-21, 27, and 42-44 are rejected under 35 U.S.C. §102(e) as being anticipated by Short (US Patent No. 6,171,820 B1) because Short discloses a method for producing a set of mutagenized progeny polynucleotides encoding a polypeptide from a parental template polynucleotide via codon site-saturation mutagenesis, wherein at each original codon there is produced at least one substitute codon encoding each of the 20 naturally occurring amino acids. It also is alleged that Short discloses the methods using plasmids and viral vectors in bacterial host cells in addressable arrays, analyzing kinetic activity as improved stability and optionally repeating the steps of the method. This rejection respectfully is traversed.

RELEVANT LAW

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. In re Spada, 15 USPQ2d 1655 (Fed. Cir, 1990), In re Bond, 15 USPQ 1566 (Fed. Cir. 1990), Soundscriber Corp. v. U.S., 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention." In re Lang, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover it is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

The Claims

Independent Claim 1 and dependent claims are directed to a process for the identification of a protein that differs in a predetermined property from a target protein. The method includes the steps of (a) producing a population of sets of nucleic acid molecules that encode modified forms of a target protein, **where all members of the set encode the same**

polypeptide, (b) **individually** introducing each set of nucleic acid molecules into host cells and expressing the encoded protein, wherein the host cells are present in an addressable array such that all host cells of one loci contain the same nucleic acid molecule express the proteins that have the same modification so that sets of proteins are produced; and(c) **individually** screening each set of encoded proteins, whereby one or more proteins that have a predetermined property that differs from the target protein is/are identified. The predetermined property is selected among a chemical, a physical and a biological property of the target protein. The identified proteins each are designated as a hit and each hit contains a mutation designated a hit position. Dependent claims specify variations of the method including methods of designing and/or synthesizing nucleic acids, methods using addressable arrays, solid supports, types of nucleic acid molecules, variations in the nucleic acids, target proteins and predetermined properties used in the methods and addition steps that can be used with the methods. Dependent claims 2-21, 32, 33 and 42-44 recite additional limitations as do independent claims 22-24 and 27.

Claim 27 and dependent claims 28 and 29 similarly recite that the nucleic acid molecules are in viral vectors and the titer of each set of vectors is assessed at step (b) and recites additional steps.

The disclosure of Short

Short is directed to mutagenesis techniques for directed evolution of proteins. The patent describes a saturation mutagenesis method that includes generating a set of modified polypeptides in which a full range of amino acid substitutions is represented at each amino acid position. As result each set contains a mixture of different modified polypeptides.

In the method as taught by Short, degenerate oligonucleotide cassettes are used to generate sets of modified polynucleotides encoding the modified polypeptides. The patent states (column 34, lines 43-49) that the polynucleotides encoding the modified polypeptides are in a single reaction vessel that contains at least 32 distinct polynucleotides encoding 20 distinct polypeptides. This mixture of polynucleotides is transformed into host cells, which express the encoded polypeptides, and the cells are screened. The host cells express mixtures of polypeptides which mixtures are screened. Hence the polypeptides are not individually expressed nor are they individually screened.

ANALYSIS

Short does not anticipate the methods as set forth in the instant claims. The claims to the methods of the rejected claims recite that the all members of each set of nucleic acid

molecules encode proteins with the same modification and include steps of individually introducing into host cells and individually screening the proteins encoded by each set of nucleic acid molecules. Hence in the instantly claimed methods each molecule is individually introduced into host cells and the encoded proteins are individually expressed, screened and tested. Neither random methods nor combinatorial methods are used in the steps of introducing into host cells and expressing the polypeptides, nor are mixtures of modified molecules screened. Each set of nucleic acids encodes a single modified form of a target protein. Thus, the sets of nucleic acids encoding proteins with the same modification are introduced **individually** into host cells. Following introduction into host cells, the encoded modified form is expressed. The encoded proteins are **individually** screened in an addressable array and proteins that have a predetermined property that differs from the target protein are identified.

In contrast, the methods disclosed by Short do not include steps of individually introducing and screening sets of nucleic acid molecules each encoding a modified protein. Short specifically states that the saturation mutagenesis described therein results in **a mixture of 32 distinct progeny nucleotides**, which are then used to produce a mixture of at least 20 different polypeptides, which are then screened.

In the instant case, each host cell at an addressed locus contains the same nucleic acid molecule, which is expressed so that all of the proteins at that address contain the same modification. Each of the proteins are individually screened.

In the method of Short, the 32 distinct progeny nucleotides **in each reaction vessel encode 20 distinct polypeptides (column 34, lines 43-60).** These mixtures of nucleic acids are amplified in a host (*E. coli*) together. They are not individually introduced into host cells nor individually expressed.

In the instantly claimed methods, each locus of the array contains a single modified nucleic acid, and upon expression, only one modified target protein is expressed. The resulting proteins are individually (each set which contains molecules of the same protein) screened. In contrast, Short teaches screening a mixture of proteins. Therefore Short does not disclose every element as claimed and does not anticipate any of claims 1-21, 27 and 42-44 nor any claims dependent thereon.

The Examiner urges that Short discloses introducing each set of nucleic acid molecules individually into host cells. Whether or not this is a correct interpretation, in the method of Short, the sets contain a mixture of nucleic acid molecules that encode mixtures of

polypeptides (at least 32 distinct polynucleotides encoding 20 distinct polypeptides (see, column 34, lines 43-49)). In the instantly claimed methods, the sets of nucleic acid molecules encode proteins with the same modification. Hence Short does not disclose introducing sets of identical nucleic acid molecules individually into host cells. The Short method generates diversity in each set.

THE REJECTIONS OF CLAIMS 22-13, 27-29, 32 AND 33 UNDER U.S.C 103(a)

Claims 22 and 23

Claims 22 and 23 are rejected under 35 U.S.C. §103(a) as being unpatentable over the combination of teachings of Short in view of Collett *et al.* (US2002/0081574B1) because Collett *et al.* teaches screening modified proteins that exhibit a 10-25 fold change in activity so that it would have been obvious to one of ordinary skill in the art to have combined the methods of Short *et al.* with those of Collett *et al.* since one of ordinary skill in the art would have been motivated to determine the activity of a modified protein. This rejection respectfully is traversed.

Claims

Independent claim 22 recites essentially the same steps as claim 1 and further recites that a "change in a predetermined property comprises a change in an activity of the target protein that is at least about 10%, 20%, 30%, 40% or 50% compared to the unmodified target protein." Independent Claim 23 recites that the change is "at least about 75%, 100%, 200%, 500% or 1000% compared to the unmodified target protein."

Analysis

As discussed above, Short does not teach all limitations of claim 1 and hence fails to teach all elements of claim 22. Collett *et al.* fails to cure the deficiencies of Short, since Collett *et al.* does not teach or suggest a method involving individually expressing and screening proteins. Therefore the combination of teachings of Short and Collett *et al.* does not result in the methods of claims 22 and 23.

Claims 24 and 27-29

Claims 24 and 27-29 are rejected under 35 U.S.C. §103(a) as being unpatentable over the combination of teachings of Short in view of Berlioz *et al.* (U.S. Patent No. 5,925,565) because Berlioz *et al.* teaches targeting proteins involved in viral replication so that it would have been obvious to one of ordinary skill in the art to have combined the methods of Short *et al.* with those of Berlioz *et al.*, which teaches that it is a goal to "create the efficient and

stable expression of genes. One of ordinary skill in the art would have been motivated to "test the efficiency and stability of vectors" This rejection respectfully is traversed.

Claims

Independent claim 24 includes the method of claim 1 and recites that the nucleic acid molecules are in viral vectors and the titer of each set of vectors is assessed at step (b).

Claim 27 similarly recites that the nucleic acid molecules are in viral vectors and the titer of each set of vectors is assessed at step (b) and recites additional steps.

Analysis

As discussed above, Short does not teach all limitations of claim 1 and hence fails to teach all elements of claim 24 or claim 27. Berlioz *et al.* fails to cure the deficiencies of Short, since Berlioz *et al.* does not teach or suggest a method involving individually expressing and screening proteins. Therefore the combination of teachings of Short and Berlioz *et al.* does not result in the methods of claims 22 and 23.

Claims 32 and 33

Claims 32 and 33 are rejected under 35 U.S.C. §103(a) as being unpatentable over the Short because use of a computer to automate a process does not without more render a claim unobvious. This rejection respectfully is traversed.

As discussed above, Short fails to teach a method that includes steps of individually expressing and screening proteins. Its method relies upon the production of mixtures of polypeptides. Short provides no teachings, nor suggestions for modifying its process. Therefore, the methods of claims 32 and 33 are not taught or suggested by Short.

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In view of the above, reconsideration and allowance are respectfully requested

Respectfully submitted,

Stephanie Seidman
Reg. No. 33,779

Attorney Docket No. 17109-002001/911
Address all correspondence to:
Stephanie L. Seidman
Fish & Richardson P.C.
12390 El Camino Real
San Diego, California 92130
Telephone: (858) 678-5070
Facsimile: (202) 626-7796
email: seidman@fr.com